Award Number: W81XWH-12-1-0581

TITLE: Endophenotypes of Dementia Associated with Traumatic Brain Injury in Retired Military Personnel

PRINCIPAL INVESTIGATOR: Kristine Yaffe, MD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education
San Francisco, CA 94121

REPORT DATE: June 2015

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;

Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
June 2015	Final	30 Sept 2012– 27 Mar 2015

4. TITLE AND SUBTITLE

Endophenotypes of Dementia Associated with Traumatic Brain Injury in Retired Military Personnel

5a. CONTRACT NUMBER
W81XWH-12-1-0581

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Kristine Yaffe, MD

email: kristine.yaffe@ucsf.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Northern California Institute for Research and Education
4150 Clement Street (151 NC)
San Francisco, CA 94121-1545

Henry Jackson Foundation for the Advancement of Military Medicine
6720A Rockledge Drive, Suite 100
Bethesda, MD 20817-1805

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Material Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT Our goal is to define the clinical phenotype of cognitive impairment in older veterans who have been exposed to TBI. Our hypothesis is that TBI in early to mid-life is associated with a clinical phenotype that has features distinguishable from AD. In the first year, we completed the screening survey portion of the study and found that over half of the veterans surveyed (n=298) had a history of head injury, with over 20% requiring hospitalization. Those with TBI were more likely to report mood, anxiety, substance use disorder, and PTSD symptoms over the course of their lifetime, have active PTSD symptoms, and have subjective memory complaints (all $p < 0.05$). A manuscript based on these results has been submitted to a peer-reviewed journal. Data collection for the cross-sectional study phase is finished (n=71 controls, n=75 TBI). The main analysis is complete and a manuscript describing the clinical phenotype of TBI in older veterans is nearly ready for submission. Another manuscript, detailing the neuropsychological results, is in preparation. The results of this study show that older veterans with past TBI have a specific clinical and neuropsychological phenotype, which has relevance for future treatment.

15. SUBJECT TERMS
Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), post-traumatic stress disorder (PTSD), aging

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	14	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Introduction

One possible long-term consequence of traumatic brain injury (TBI) is dementia. TBI in early and mid-life is associated with an increased risk of late-life dementia, with relative risks in the order of 2.5 to 5.0 [1-3]. Military veterans are at high risk of TBI during combat as well as during peacetime service [4]. The goal of this project is to define the clinical phenotype of late-life dementia in veterans who have been exposed to TBI. Our hypothesis is that TBI in early to mid-life is associated with a clinical phenotype that has features distinguishable from Alzheimer's disease (AD). Specifically, we hypothesize that: 1) veterans with TBI-associated cognitive impairment will have higher levels of symptoms of depression, anxiety, and Parkinsonism compared to veterans with cognitive impairment/dementia who have not experienced a TBI, and 2) veterans with TBI-associated cognitive impairment will have prominent deficits in executive function, compared to veterans with cognitive impairment who have not had a TBI. This cross-sectional study will lead to a better understanding of the features of TBI-associated cognitive impairment and dementia in retired military veterans. The project will develop clinical criteria to allow accurate and early diagnosis and is critically important to the Department of Defense, the Veterans Administration, as well as to society at large.

Key Words

Traumatic brain injury (TBI), dementia, chronic traumatic encephalopathy (CTE), post-traumatic stress disorder (PTSD), aging

Overall Project Summary

Task 1: Screen retired military service men and women at each site [Armed Forces Retirement Home (AFRH), Washington, DC and Veterans Home of California-Yountville (VHC-Yountville)]

Subtask 1a. Planning and Regulatory Review

In the first two quarters of the project we received full regulatory approval for both sites. The California site had two separate protocols approved. For the screening survey, the protocol titled "Prevalence of Traumatic Brain Injury, Memory Problems, and Post Traumatic Stress in Retired Military Servicemen and Women" received University of California, San Francisco (UCSF) Committee on Human Research (CHR) approval on June 20, 2012. This protocol was reviewed and approved by the US Army Medical Research and Material Command (USAMRMC), Office of Research Protection (ORP), and Human Research Protection Office (HRPO), and received final approval on February 4, 2013. The protocol received continuing renewal approval from UCSF on May 22, 2013 and the official continuing review report was submitted to

USAMRMC HRPO. “Endophenotypes of Dementia Associated with Traumatic Brain Injury in Retired Military Personnel”, the cross-sectional study protocol, received UCSF CHR approval on October 11, 2012 and USAMRMC, ORP, and HRPO approval on February 4, 2013. The protocol received continuing renewal approval from UCSF on October 4, 2013 and the official continuing review report was submitted to USAMRMC HRPO. The sub-site Uniformed Services University of the Health Sciences (USUHS) received approval for the combined survey and study protocol “Endophenotypes of Dementia Associated with Traumatic Brain Injury in Retired Military Personnel” from the USUHS Institutional Review Board on March 20, 2013. USAMRMC, ORP, and HRPO second level approval was received for the sub-site on April 17, 2013.

The subcontract with the Henry Jackson Foundation (HJF) was executed on January 30, 2013. Once the grant was awarded, we initiated monthly conference calls with the sub-site to discuss study initiation and progress as well as refining the study protocol, measurements, operations manual, and study survey. Both sites held meetings with administrators at the VHC-Yountville and AFRH to discuss study set-up and logistics. Once the screening survey was underway, our monthly conference calls focused on writing and refining the case report forms, order of tests, and manual of operations for the second phase of the study. Dr. Kramer trained all study personnel on the administration of the neuropsychological tests; Dr. Kramer traveled to HJF and select HJF study staff traveled to UCSF for training.

Subtask 1b. Screen retired service members at AFRH and VHC-Yountville

Data collection for the survey screening portion of the study (Phase 1) is complete. Approximately one-third of individuals residing in independent living at VHC-Yountville and AFRH completed surveys for a combined total of 298. Eighty-four percent of survey participants were white; 90% were male, and the mean age was 78.5 years ± 10.7. TBI exposure was defined as head injury resulting in symptoms (including being dazed, amnesia for the injury, memory gaps, loss of consciousness) or subsequent hospitalization. Current post-traumatic stress disorder (PTSD) symptoms were assessed using the PTSD-2 Checklist (PCL-2). Participants reported lifetime presence of psychiatric diagnoses and current severity of subjective memory complaints, and completed objective cognitive orientation items.

TBI with head injury symptoms only was found in 34.6% (n = 103); 20.8% (n = 62) had TBI with subsequent hospitalization. 26.8% had military TBI; almost 50% had civilian TBI; and 13.4% had both military and civilian TBI (see Table 1 below). Table 2 shows the baseline characteristics of participants in each of the TBI groups.

Table 1. Prevalence of TBI groups and head injury symptoms.

	Any cause*, N (%)	Military, N (%)	Civilian, N (%)
Exposure to head injury			
None or head injury without symptoms	124 (41.6)	218 (73.2)	150 (50.3)
TBI with only head injury symptoms	103 (34.6)	42 (14.1)	95 (31.9)
TBI with subsequent hospitalization	62 (20.8)	20 (6.7)	48 (16.1)
Head injury symptoms			
Dazed, confused, seeing stars	136 (45.6)	52 (17.4)	114 (38.3)
Not remembering the injuries	55 (18.5)	15 (5.0)	46 (15.4)
Memory gaps	63 (21.1)	23 (7.7)	50 (16.8)
Duration of LOC	90 (30.2)	31 (10.4)	72 (24.2)
<30 mins	51 (17.1)	13 (4.4)	33 (11.1)
30 mins-24hrs	10 (3.4)	5 (1.7)	7 (2.3)
24 hrs+	12 (4.0)	2 (0.7)	12 (4.0)
Unknown duration	25 (8.4)	11 (3.7)	22 (7.4)

*If subjects had both civilian and military TBI of differing severity, the more severe category was used for TBI status.
%'s based on total number of participants, 298. Completed responses *n* = 281-294.
LOC = loss of consciousness.

Table 2. Baseline Characteristics by TBI Status.

Characteristics mean ± SD, N (%)	**No TBI*** (n = 124)	**TBI with symptoms** (n = 103)	**TBI with hospitalization** (n = 62)	**P-value for trend**
Age, years	81.2 (9.1)	78.0 (10.1)	75.1 (12.1)*	0.001
Male gender	105 (84.7)	97 (94.2)*	59 (95.2)*	0.006
White	98 (79.0)	89 (86.4)	54 (87.1)	0.44
Currently married	13 (10.5)	16 (15.5)	9 (14.5)	0.46
Education (> high school)	56 (45.2)	59 (57.3)	33 (53.2)	0.19
Military service, years	12.1 (8.9)	7.0 (7.6)*	7.3 (7.3)*	<0.001
Junior enlisted rank (E1-E4)	28 (22.6)	43 (41.7)*	29 (46.8)*	0.005
Any military injury	36 (29.0)	61 (59.2)*	36 (58.0)*	<0.001

*P < 0.05 when compared to non-TBI group as per post-hoc analyses.

Compared to those without TBI, those with TBI had higher levels of depression (61.3% for hospitalization group vs. 55.3% for head injury symptom group vs. 24.2% for non-TBI group, P < 0.001) and PTSD (37.1% for hospitalization group vs. 21.4% head injury symptoms group vs. 8.1% for non-TBI group, P < 0.001). Figure 1 shows that individuals with TBI had more active psychiatric symptoms and were more likely to have multiple psychiatric diagnoses compared to those with no head injury. Severity of TBI was associated with higher severity scores of current

PTSD symptoms on PCL-2 (3.9 ± 2.2 for hospitalization group vs. 3.2 ± 2.0 for head injury symptom group vs. 2.7 ±1.6 for non-TBI group, P < 0.001) (See Figure 2).

FIGURE 1. Severity of Psychiatric Diagnosis by TBI Status.

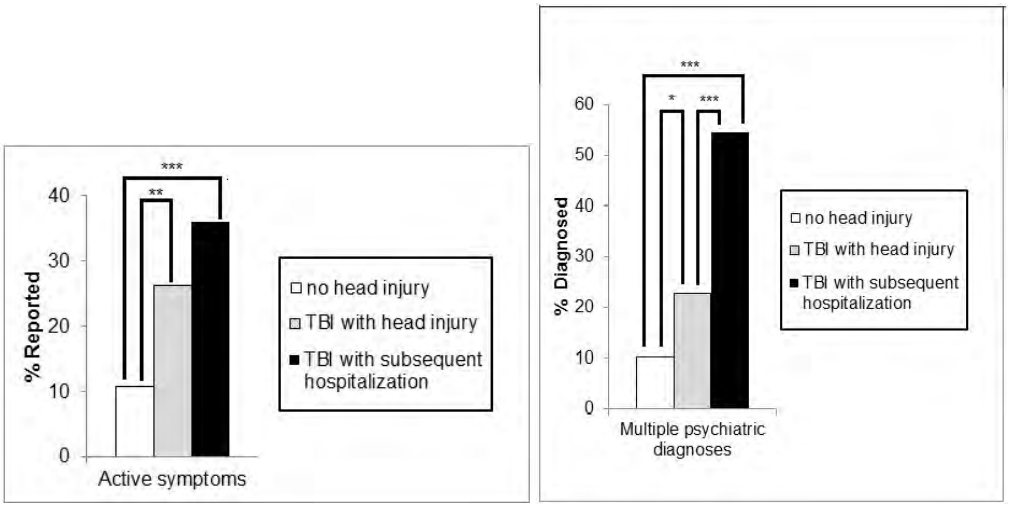
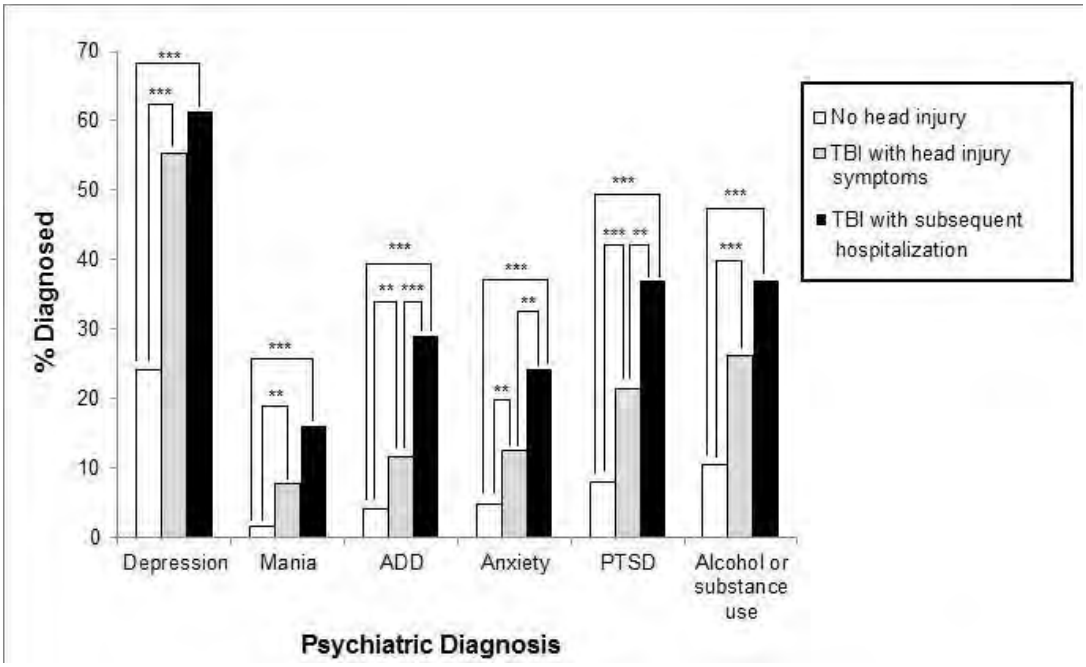


Figure 1A. Figure 1B.

*P < 0.10, **P < 0.01, ***P < 0.001

FIGURE 2. Psychiatric Diagnosis by TBI Status.



ADD = attention-deficit disorder
Post-traumatic stress disorder = PTSD
*P < 0.10, **P < 0.01, ***P < 0.001

Compared to those without TBI, participants with TBI and subsequent hospitalization were more likely to have more subjective memory complaints (25.8% for hospitalization group vs. 9.7% for non-TBI, P = 0.008); this trended towards significance for the TBI with head injury symptom group (19.4%, P = 0.051). There were no significant differences in performance on orientation items (P = 0.32).

From the screening survey we have shown that TBI is a common occurrence in the older veterans residing in veterans homes, affecting over half of the population, and is associated with a higher history of psychiatric disorders and current cognitive symptoms. An abstract with this data was presented at the 2013 Alzheimer's Association International Conference in Boston, MA, and a manuscript describing the results has been submitted to a peer-reviewed journal.

Task 2. Enroll retired service members at AFRH and VHC-Yountville

Potentially eligible participants were identified using information from: (1) the survey in which participants consented to be contacted for a future study, and (2) chart review through an IRB-approved Waiver of Authorization for Recruitment. The potentially eligible participants were contacted and asked if they were interested in taking part in the cross-sectional study. After a thorough explanation of the study and procedures, those interested in participating were scheduled for a study visit and consented before any study procedures took place. The inclusion and exclusion criteria are listed in the appendix. If, upon learning further information, the patient does not meet eligibility criteria, they were considered a screen failure and do not go through study procedures.

Subtask 2a. Evaluate both cases and controls

Data for each participant (TBI or control) was collected over two separate appointments, each taking no longer than 90 minutes. The first visit involved signing the consent and HIPAA documents, gathering basic demographic and medical history data, various health and lifestyle questionnaires, and a neurological examination. All the neuropsychological tests took place at the second visit. As of 10/31/14, data collection is complete. We have collected data from 146 individuals, 75 with a history of TBI requiring medical care, and 71 controls.

The main analysis for the project is complete and a manuscript describing the clinical phenotype of TBI in older veterans is nearly ready for submission. Another manuscript, detailing the neuropsychological results, is in preparation. Preliminary results on the first 118 participants (61 TBIs and 57 controls) were presented at the Alzheimer's Association

International Conference, July 2014. Updated results with the full dataset of 146 participants will be presented at the Alzheimer's Association International Conference, July 2015.

We enrolled 75 participants with a history of TBI. Some basic characteristics of their head injuries are listed in **Table 1**. The majority of participants experienced more than one TBI in their lifetime, and reported loss of consciousness for at least one TBI. In total, 159 symptomatic head injuries were recorded for these 75 participants. The breakdown of the head injuries by mechanism is listed in the table. Each individual's most severe head injury was categorized by severity; 68% had mild, 20% had moderate, and 12% had severe.

Table 1: TBI Characteristics, n=75

Characteristic	Mean (SD) or %
Age at first TBI, years	26.9 (21.5)
Age at most recent TBI, years	44.4 (24.8)
Participants with > 1 TBI	61.3%
At least 1 TBI with LOC	72.0%
Military TBI	28.0%
Mechanism of injury (all TBIs)	
Falls	34.6%
Blunt Force Trauma	34.0%
Motor Vehicle or Bicycle Accident	24.5%
Blast Injuries	5.0%
Other	1.9%
Severity (most severe per person)	
Mild	68%
Moderate	20%
Severe	12%

LOC = loss of consciousness

Basic demographic and medical history comparisons between participants with TBI and controls are shown in **Table 2**. TBI participants were younger ($p = 0.06$), less likely to be a minority, and more likely to have a history of diabetes (both $p < 0.05$). All subsequent analyses are adjusted for age, gender, race, years of education, history of diabetes, and study site. Behavioral and functional variables are reported in **Table 3**. Individuals with TBI history participated in fewer intellectual and leisure activities ($p = 0.02$), had greater functional impairment ($p = 0.04$), and reported more subjective memory loss ($p = 0.048$). TBI participants endorsed more current depression ($p = 0.047$) and PTSD symptoms ($p = 0.02$), although both are far below clinical criteria for diagnosis. Sleep quality, physical activity, and satisfaction with life did not differ between the two groups. Psychiatric and cognitive results in TBI participants vs. controls are

also shown in **Table 3**. Participants with TBI had a greater history of depression and substance abuse (both $p < 0.01$). No differences between groups were found for history of anxiety, PTSD, or bipolar disorder. General cognition, measured by MMSE, was slightly higher in controls participants compared to those with past TBI ($p = 0.03$).

To examine the neuropsychological differences between veterans with and without TBI, we calculated composite z-scores for three cognitive domains (learning/memory, language, and processing speed/executive functioning). The results are shown in **Table 4**. Learning/memory and language composite scores did not differ between the groups, but processing speed/executive functioning composite score was significantly lower in participants with TBI ($p<0.01$). This association persisted after additionally adjusting for psychiatric comorbidities ($p<0.05$).

Table 2. Demographics

Mean (SD) or %	Control *N = 71*	TBI *N = 75*	P-value
Age, years	78.9 (8.8)	76.5 (10.2)	0.06
Gender, males	88.7%	92.0%	0.27
Race, minority	12.7%	2.7%	**0.01**
Education, years	14.6 (2.7)	14.3 (2.6)	0.26
Military Service, years	10.9 (8.9)	11.1 (8.9)	0.44
Medical History			
Hypertension	78.9%	77.0%	0.40
Stroke	12.7%	13.5%	0.44
Diabetes	18.3%	38.7%	**0.003**

Table 3: Outcomes

Mean (SD) or %	Control *N = 71*	TBI *N = 75*	P-value*
Neurological			
UPDRS-Motor†	8.9 (8.4)	10.2 (8.3)	0.18
Behavioral/Functional			
Pittsburgh Sleep Quality Inventory†	6.7 (5.3)	8.4 (5.4)	0.21
Intellectual/Leisure Activities Scale	29.5 (8.5)	25.4 (9.6)	**0.02**
RAPA 1 (physical activity)	3.6 (1.3)	3.3 (1.4)	0.61
RAPA 2 (strength/flexibility)	1.2 (1.4)	1.3 (1.3)	0.16
Functional Activities Questionnaire†	0.49 (1.7)	1.28 (3.7)	**0.04**
Everyday Cognition†	1.2 (0.3)	1.5 (1.3)	**0.048**
Satisfaction with Life Scale	28.1 (5.7)	25.5 (6.4)	0.09
GDS†	1.12 (1.6)	2.02 (2.8)	**0.047**
PCL-C†	19.5 (6.6)	23.1 (8.5)	**0.02**
Psychiatric History			
Depression	18.3%	44.0%	**0.002**
Anxiety	15.7%	26.7%	0.29
PTSD	8.5%	17.6%	0.10
Bipolar Disorder	4.2%	8.0%	0.40
Substance abuse	20.0%	46.7%	**0.003**
Cognitive			
General Cognition (MMSE)	28.2 (1.5)	27.5 (2.6)	**0.03**

UPDRS-Motor = Unified Parkinson's Disease Rating Scale-Motor; RAPA = Rapid Assessment of Physical Activity; GDS=Geriatric Depression Scale; PCL-C=PTSD Checklist-Civilian; PTSD=Post-Traumatic Stress Disorder

*adjusted for age, gender, race, education, diabetes, site

† higher score is worse

Table 4: Neuropsychological Test Composite Scores

Mean (SD)	Control *N = 71*	TBI *N = 75*	Model 1	Model 2
Composite Z Scores				
Learning and Memory	-0.013 (0.85)	0.018 (0.97)	0.97	0.71
Language	0.048 (0.82)	-0.018 (0.84)	0.35	0.71
Processing Speed/Executive Function	0.124 (0.78)	-0.153 (0.99)	**0.005**	**0.03**
EXAMINER Composite Z Scores				
Executive Composite	0.110 (0.97)	-0.116 (1.02)	0.23	0.47
Fluency Factor	0.040 (1.03)	-0.041 (1.02)	0.84	0.96
Cognitive Control Factor	0.138 (0.93)	-0.146 (1.06)	***0.07***	0.21

Model 1: adjusted for age, gender, race, education, diabetes, site

Model 2: Model 1 + substance abuse history, depression symptoms, PTSD symptoms

Key Research Accomplishments

- Screening survey developed, administered to 298 veterans, and data analyzed.
- Survey data manuscript currently under review.
- Cross-sectional study completed with clinical and neuropsychological data from nearly 150 veterans.
- Cross-sectional data analysis completed and two manuscripts in preparation.

Conclusion

In the first year of the project we developed and administered a survey to nearly 300 veterans residing in two veterans homes. We found that TBI is a common occurrence in the older veterans residing in veterans homes, affecting over half of the population, and is associated with a greater history of psychiatric disorders and current cognitive symptoms. The study results indicate that this understudied group of older veterans is likely a fruitful population for examining TBI-related cognitive impairment.

In this past year we completed data collection for the cross-sectional study, establishing a cohort of nearly 150 veterans, approximately half with a history of TBI. Results indicate that the participants with TBI history are likely to have more behavioral and psychiatric difficulties and lower scores on tests of executive function and processing speed, even after adjusting for confounding variables. We are currently writing up the results of the final study in two separate manuscripts.

Understanding the features of cognitive impairment in retired military veterans, and developing clinical criteria to allow accurate and early diagnosis is critically important to the Department of Defense, the Veterans Administration, as well as to society at large. For service members at increased risk of AD-type neurodegeneration as a consequence of their service in combat, early recognition is essential in order to implement preventive therapies.

Publications, Abstracts, and Presentations

1. Wang S, Culver C, Diaz-Arrastia R, McCormack M, Awoke S, Yaffe K. Traumatic brain injury and comorbid neuropsychiatric symptoms in an older veteran population. Alzeimer's Association International Conference; 2013; Boston, MA: Alzheimer's & Dementia 2013; 9(4)P542. DOI: 10.1016/j.jalz.2013.04.295
2. Peltz C, Kramer J, Kenney K, Diaz-Arrastia R, Yaffe K. Cognitive effects of TBI in older veterans. Alzeimer's Association International Conference; 2014; Copenhagen, Denmark: Alzheimer's & Dementia 2014; 10(4):P205. DOI:10.1016/j.jalz.2014.04.258
3. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. Neurology 2014; 83(4):312-319.

4. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. Dementia risk after traumatic brain injury versus non brain trauma: the role of age and severity. JAMA Neurology 2014; 71:1490-1497.
5. Yaffe K, Peltz C, Gardner R, Kenney K, Kramer J, & Diaz-Arrastia R. Clinical Profile of Older Veterans with Remote TBI. Alzeimer's Association International Conference; 2015; Washington, DC: Alzheimer's & Dementia 2015.
6. Wang S, Culver C, Peltz C, Diaz-Arrastia R, Kenney K, Kramer J, Awoke S, Yaffe K. Traumatic Brain Injury and Comorbid Neuropsychiatric Symptoms in an Older Veteran Population. Under Review.

Inventions, Patents, and Licenses

N/A

Reportable Outcomes

N/A

Other Achievements

- Utilizing pilot data, we applied to the DOD to expand on this project in order to obtain blood samples for biomarker analysis and increase our cohort to include participants with mild AD. Dr. Kristine Yaffe will serve as the PI of the project with Dr. Ramon Diaz-Arrastia as Co-PI. The project has been funded and we received the Notice of Award on 9/22/14. There is no scientific or funding overlap with this project.

References

1. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry 2003;74:857-862.
2. Guo Z, Cupples LA, Kurz A, et al. Head injury and the risk of AD in the MIRAGE study. Neurology 2000;54:1316-1323.
3. Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000;55:1158-1166.
4. Okie S. Traumatic brain injury in the war zone. N Engl J Med 2005;352:2043-2047.

Appendix

Inclusion Criteria

- TBI Participants:
  - Aged 50-95
  - Resident in the independent living facility at the VHC-Yountville or the AFRH-Washington D.C.
  - Can speak, read, and understand English
  - Capacity to provide consent to participate in research
  - MMSE score ≥ 20
  - History of traumatic brain injury: required to have sought medical treatment (ER visit, doctor visit, hospitalization) after a head injury
- Controls (without a history of TBI):
  - Aged 50-95
  - Resident in the independent living facility at the VHC-Yountville or the AFRH-Washington D.C.
  - Can speak, read, and understand English
  - Capacity to provide consent to participate in research
  - MMSE score ≥ 20
  - No history of TBI or concussion (defined as no head injury resulting in being dazed, having a memory gap, loss of consciousness, or medical treatment)

Exclusion Criteria

- TBI Participants:
  - History of penetrating brain injury
  - Currently active disabling neurological or psychiatric condition (such as epilepsy, multiple sclerosis, cortical stroke, hypoxic-ischemic encephalopathy, encephalitis or schizophrenia)
  - Lack of competence to provide consent to participate in research
  - No verbal and oral fluency English
  - Non-correctable vision or hearing impairments (severe enough to impair testing)
- Controls (without a history of TBI):
  - Currently active disabling neurological or psychiatric condition (such as epilepsy, multiple sclerosis, cortical stroke, hypoxic-ischemic encephalopathy, encephalitis or schizophrenia)
  - Lack of competence to provide consent to participate in research
  - No verbal and oral fluency English
  - Non-correctable vision or hearing impairments (severe enough to impair testing)